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Bad air gets under your skin

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Short Title: Bad air gets under your skin

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"Few risks have a greater impact on global health today than air pollution; the evidence signals the need for concerted action to clean up the air we all breathe." – Dr. Maria Neira, Director of WHO's Department for Public Health, Environmental and Social Determinants of Health.

The World Health Organisation (WHO) released a report in 2014 indicating that 3.7 million premature deaths globally were attributable to ambient air pollution in 2012 (1). Their data more than doubled previous estimates and placed air pollution as the world's largest environmental health risk factor. This essay focuses on ambient pollution, which refers to outdoor air pollution, and assesses the current evidence regarding the effects of environmental pollutant exposure on skin health.

The majority of outdoor pollutants come from anthropogenic sources such as vehicle emissions, fossil fuel combustion, forest fires and industrial processes (2). These noxious substances are naturally present in the atmosphere at low concentrations, but in areas rich in industrialisation, their concentrations often exceed guideline amounts. The WHO has released figures showing that in urban areas which monitor air pollution levels, greater than 80% of people are exposed to levels of pollution which exceed WHO limits (1).

Outdoor pollution comes from a combination of fixed sources, such as factories, and mobile sources, such as road and air traffic. This combination of sources produces primary and secondary pollutants (2). Primary pollutants can be divided into two groups: particulate matter (PM) and gases (CO_2, CO, NO_2, NO, NO_x, SO_2) (2). Secondary pollutants such as ozone are formed from photochemical reactions between the primary pollutants, heat and UV radiation. Other environmental air pollutants of major public concern include polycyclic aromatic hydrocarbons (PAHs) and activation of aryl hydrocarbon receptors (AhR).

As air pollution has become a growing concern in today's society, there has been increasing research on the effects of ambient pollution on health. Many studies have demonstrated the acute and chronic effects of exposure to environmental pollutants on morbidity and mortality (3). By comparison there is a paucity of research investigating the effects of ambient pollutants on human skin. The skin serves as an environmental interface, providing a protective envelope and as a result, is a major target for toxic insult by a broad spectrum of physical and chemical agents in ambient pollution that are capable of altering its structure and function.

Phthalates

It is known that phthalates are widespread contaminants in both indoor and outdoor environments but the plastic industry continues to generate phthalates every year on a considerable scale (4). The toxicants can be delivered into the body via inhalation, dietary intake, and skin absorption. In our daily lives, we can be exposed to this compound from building material, household furnishing, soil, and dust (4). Pan and colleagues describe how phthalates often exert their cutaneous response through the use of cosmetics and topical uses because they are not chemically bound to most products, easily becoming released to the skin. Using mice or pig models they found that infants and children were high risk populations for the xenobiotic toxicity on skin. Although they primarily focused on cosmetics, their results highlighted that the skin could be a significant route for phthalate intake. The xenobiotic can be found in dust particles and ambient air as a result of factory pollution. Exposure to phthalates can disrupt the differentiation and proliferation of keratinocytes, impairing barrier function (4). A further concern of phthalate exposure is potential for tumourigenesis. Protein biomarkers of epidermal malignancy from phthalate exposure include HSP27 and cytokeratin. HSP27 was overexpressed with cutaneous phthalate exposure, suggesting tumourigenesis of squamous cell carcinoma (4). However, this clearly is an area of research that requires further investigation particularly as animal skin and localization of acute toxicity can be limiting factors for human translational studies.

Particulate matter (PM)

Particulate matter is a complex mixture of particles suspended in air which are produced by a variety of natural and anthropogenic activities (3). Major sources of PM include open fires, industrial facilities, power plants and vehicle exhausts (3). PM can be divided into three types depending on size; ultrafine particles (UFP), fine particles ($PM_{2.5}$) and coarse particles (PM_{10}). The size and composition of PM both influence their effects on health. Due to the increase in urbanisation and industrial processes PM are widely implicated in contributing to ambient pollution worldwide. Given the growing concern regarding PM, the WHO has produced guidelines suggesting concentration limits for fine and coarse PM (5). Global estimates of PM

concentrations have recently been measured by satellite imagery. This has demonstrated that certain countries, in particular China and India, have annual PM concentrations that far exceed the limits set by the WHO (2).

Studies have shown that exposure to ambient PM is associated with increased morbidity and mortality (3). There is growing evidence on the negative effects of outdoor particulate pollutants on human skin. One study investigated the effects of urban particulate pollutants, including ultrafine particles, on symptom severity in children with atopic dermatitis. They measured daily concentrations of ambient particulate pollution and found a significant association between the daily concentration of PM and increased symptom severity. Their results suggested that ambient PM might exacerbate symptoms of atopic dermatitis in children (5). A longitudinal study in Korea evaluated the clinical effects of outdoor air pollutants in patients with atopic dermatitis. Researchers measured daily outdoor concentrations of PM, nitric oxides and volatile organic compounds to estimate each patient's exposure to air pollution. They found a direct correlation between outdoor particulate concentration and presence of symptoms in AD, demonstrating that ambient air pollution was an aggravating factor for patients with atopic dermatitis (5).

Aryl hydrocarbon receptor (AhR)

One of the mechanisms by which ambient air pollution can induce skin damage includes activation of the aryl hydrocarbon receptor (AhR) (6). Ambient air pollutants generate free radicals that also include the cutaneous inflammatory cascades, activating AhR dependent mechanisms and altering cutaneous microflora (6). AhR is a ligand-activated transcription factor found in various skin cells including keratinocytes, fibroblasts and melanocytes. Non-activated AhR resides in a cytosolic multiprotein complex and upon ligand binding, the complex dissociates, causing AhR translocation to the nucleus where it stimulates gene expression of those containing the xenobiotic responsive element (XRE). Activation of AhR plays a role in mediating the biochemical and toxic effects of air pollutants such as dioxins, ozone and PAHs and can influence cell biological endpoints such as growth and differentiation (6).

Studies have demonstrated the involvement of AhR activation in various skin conditions. One study which examined the involvement of AhR activation in transgenic mice found that activation of AhR transcription led to inflammatory skin lesions which mimicked atopic dermatitis. Microarray gene analysis of the mouse skin show up-regulation of genes associated with inflammation (6). The results of this work show that activation of AhR may be involved the development of inflammatory skin disease.

Polycyclic aromatic hydrocarbons (PAHs)

PAHs are ubiquitous constituents of ambient pollution that have been shown to have serious carcinogenic effects (5). They are generated during the incomplete combustion of organic matter and co-exist in complex mixtures with airborne particulate matter or gases. The majority of outdoor PAHs are derived from coal tar, diesel exhausts and cigarette smoke (5). In addition to inhalation, dermal exposure to PAHs represents an important route as they can be

easily absorbed through the skin (2). Numerous studies support the association between PAHs and adverse effects on skin health.

A study by Vierkötter and colleagues examined the association between extrinsic skin ageing and air pollution by clinically assessing Caucasian women living in urban and rural areas in Germany (6). Their results demonstrated that ambient pollution exposure significantly correlated with extrinsic skin aging, in particular pigment spots and wrinkles. They found that exposure to soot, a mixture of carbon particles covered with PAH, was associated with a 20% increase in pigmented spots on the forehead and cheeks (6). One study examined the effects of single PAH's (benzo(a)pyrene and dibenzo(def,p)chrysene) and environmental PAH mixtures using a mouse skin tumour model. Topical application of both single PAHs and the PAH mixtures resulted in the development of papillomas, carcinoma in situ and squamous cell carcinoma (5). The pattern of skin cancer and the rate of tumour progression differed according to the type of PAH mixture. Absorbed PAHs mediate some of their effects by acting as potent ligands for the AhR. The interaction between PAH and the AhR induces the production of highly carcinogenic metabolites and promotes tumourigenesis (2). One study used a mouse model to examine the role of the AhR in PAH-mediated carcinogenesis. They found that exposure to PAH resulted in the development of squamous cell carcinomas in AhR-positive mice however no tumours were found on the skin of AhR-deficient mice (5).

PAHs may be metabolically activated to generate reactive oxygen species (ROS) that can react to form bulky DNA adducts or strand breaks on cellular DNA (7). ROS are free radicals that contribute to oxidative stress, a resultant damage that arises due to an increase in destructive free radicals and reduction in protection from antioxidants (5). PAH has been shown to be increase heme oxygenase expression, a sensitive marker for oxidative stress (5). The ability of PAHs to increase ROS production is detrimental to skin and can result in adverse cosmetic effects. Accumulation of oxidative stress secondary to excessive ROS can lead to premature skin ageing (5).

Ozone and Nitrogen Dioxide

Ground level ozone (O_3) generation is a major component of smog and is formed as a result of a photochemical reaction between O_2 and pollutants such as hydrocarbons and nitrous oxides which is facilitated by sunlight. O_3 targets the skin surface and does not directly exert an effect on skin cells. The toxic effects of O_3 are mediated through free radical reactions that are achieved either directly by oxidation of biomolecules to generate reactive oxygen species or by the radical-dependent production of cytotoxic, non-radical molecules (aldehydes) (8). Biological studies examining the effects of ozone (O_3) on the skin have shown that O_3 can have a deleterious effect on skin health (9). Studies have shown that exposure to ozone results in dose dependent depletion of antioxidants vitamin C and E and (6). Furthermore, it has been demonstrated that the addition of vitamin C and E can prevent the formation of oxidation products thus protecting skin from environmentally induced oxidative stress (6). A study conducted in China looked at the correlation between exposure to ambient pollution and visits to the emergency department for skin problems. They found that an increase in the level of ozone corresponded with an increased number of skin complaints including urticaria, eczema,

contact dermatitis and skin infections (2). Research conducted in France investigated the relationship between the level of ambient pollution and visits to the general practitioner. Their results identified that an increase in zone and PM was significantly associated with an increased incidence of skin rash as well as other medical problems (2). These findings demonstrate the link between exposure to ozone and adverse effects on cutaneous health.

In addition to ground level ozone, ambient pollution is characterised by increased levels of nitrogen dioxide. A recent study examined the link between nitrogen dioxide exposure and the formation of lentigines, a hallmark of aged skin, in Caucasian and Asian women. The results demonstrated that exposure to ambient nitrous dioxide was significantly associated with increased numbers of cheek lentigines in both cohorts thus demonstrating a link between ambient pollutants and extrinsic skin aging (10). Another study investigated the effect of exposure to nitrogen dioxide on epidermal barrier function and transepidermal water loss in patients with atopic eczema (11). The results showed that short term exposure to nitrogen dioxide lead to skin surface changes and disturbance of epidermal barrier function. NO_2 causes oxidative damage, generating free radicals that can oxidize amino acids in tissue proteins and initiates lipid peroxidation of polyunsaturated fatty acids in pulmonary cell membranes (11). A similar mechanism may be accountable for the effect of ambient nitrogen dioxide on skin. The results of these studies illustrate the influence of ambient nitrogen dioxide pollutants on skin.

Summary

Air pollution is increasing beyond previous estimates and is now viewed as the world's largest environmental health risk factor. In this essay, the key nature of air pollution and effects of air pollution on skin are assessed by providing a perspective on environmental pollutant exposure and cutaneous health. Although there is comparably less research on the impact of outdoor pollution on skin, there is convincing evidence presented here demonstrating the adverse effects of ambient pollutants on skin integrity. Further experimental studies are required to assess the deleterious effects of short and long term ambient pollution exposure on skin. This type of evidence could be used to develop potential strategies to prevent the effects of bad air getting under our skin.

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Conflicts of Interest

The authors report no conflicting interest

References

1. WHO report on outdoor air pollution. http://www.who.int/phe/health_topics/outdoorair/en/

2. Krutmann J, Liu W, Li L, et al. Pollution and skin: from epidemiological and mechanistic studies to clinical implications. Journal of dermatological science 2014: 76: 163-168.
3. Kampa M, Castanas E. Human health effects of air pollution. Environmental pollution 2008: 151: 362-367.
4. Pan T L, Wang P W, Aljuffali I A, Hung Y Y, Lin C F, Fang J Y. Dermal toxicity elicited by phthalates: evaluation of skin absorption, immunohistology, and functional proteomics. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 2014: 65: 105-114.
5. Kim K E, Cho D, Park H J. Air pollution and skin diseases: Adverse effects of airborne particulate matter on various skin diseases. Life sciences 2016: 152: 126-134.
6. Mancebo S E, Wang S Q. Recognizing the impact of ambient air pollution on skin health. Journal of the European Academy of Dermatology and Venereology : JEADV 2015: 29: 2326-2332.
7. Valavanidis A, Vlachogianni T, Fiotakis K, Loridas S. Pulmonary oxidative stress, inflammation and cancer: respirable particulate matter, fibrous dusts and ozone as major causes of lung carcinogenesis through reactive oxygen species mechanisms. International journal of environmental research and public health 2013: 10: 3886-3907.
8. Valacchi G, Sticozzi C, Pecorelli A, Cervellati F, Cervellati C, Maioli E. Cutaneous responses to environmental stressors. Annals of the New York Academy of Sciences 2012: 1271: 75-81.
9. Valacchi G, Fortino V, Bocci V. The dual action of ozone on the skin. The British journal of dermatology 2005: 153: 1096-1100.
10. Huls A, Vierkotter A, Gao W, et al. Traffic-Related Air Pollution Contributes to Development of Facial Lentigines: Further Epidemiological Evidence from Caucasians and Asians. The Journal of investigative dermatology 2016: 136: 1053-1056.
11. Eberlein-Konig B, Przybilla B, Kuhnl P, et al. Influence of airborne nitrogen dioxide or formaldehyde on parameters of skin function and cellular activation in patients with atopic eczema and control subjects. The Journal of allergy and clinical immunology 1998: 101: 141-143.